UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Washington, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Antimicrobial Division

January 10, 2017

DP BARCODE: 436502

MRID(s): 499978-01

SUBJECT: HM 4072 Antimicrobial

REG. NO. OR FILE SYMBOL: 83019-4

DOCUMENT TYPE: Acute Toxicity Review

Manufacturing-use [ ] OR **End-use Product [X]**

INGREDIENTS:

PC Code(s)	CAS Number(s)	Active Ingredient(s):
107401	27668-52-6	1-Octadecanaminium, N,N-dimethyl-N-(3-(trimethoxysilyl)propyl)-,chloride

TEST LAB: Stillmeadow, Inc

SUBMITTER: Biosafe, Inc

GUIDELINE(s): 870.1100, 870.1200, 870.1300, 870.2400, 870.2500, 870.2600.

COMMODITIES: N/A

REVIEWER: Boris S. Yurchak **ORGANIZATION:** AD/PSB/CTT

APPROVER: Jenny J. Tao **APPROVED DATE:** 01/11/2017

COMMENT: This product is for non-food use

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MEMORANDUM

SUBJECT: Acute Toxicity Review for EPA Reg. No. 83019-4
Product Name: HM 4072 Antimicrobial
DP Barcode: 436502

TO: Rose Kyprianou / Timothy Young
Regulatory Management Branch II
Antimicrobials Division (7510P)

FROM: Boris S. Yurchak, Chemist
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510P)

THRU: Jenny J. Tao, Sr. Toxicologist
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510P)

APPLICANT: Biosafe, Inc
Action code: (A676) Product Reregistration Decision
Due out date: January 31, 2017

PRODUCT FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
3-(trimethoxysilyl) propyl dimethyloctadecyl ammonium chloride	72.0
Other Ingredient(s)*	28.0
TOTAL	100.0

*Contains over 12% Methanol

BACKGROUND:

The registrant is submitting 6 acute toxicity studies to support the reregistration of the subject product, *HM 4072 Antimicrobial*, EPA Reg. No. **83019-4**. All studies are described in MRID 49997801. The studies were conducted by Stillmeadow, Inc. The test material used in the studies was *Ztrex 72 Antimicrobial Agent MUP* (EPA Reg. No. 48937-1) that is substantially similar to the subject product. The product is used to control mold, mildew and algae.

The data package included:

1. Cover letter from Registrant to EPA, dated 09/22/2016
2. Application for pesticide registration, Form 8570-1
3. Basic Confidential Statements of Formula (CSF), dated 07/23/2013
4. Accepted label, dated 09/24/2014

FINDINGS:

1. All acute toxicity studies cited are found to be acceptable.
2. The acute toxicity profile for EPA Reg. No. **83019-4** is currently:

GRN	Study	MRID	Toxicity Category	Status
870.1100	Acute Oral Toxicity	49997801	IV	Acceptable
870.1200	Acute Dermal Toxicity	49997801	IV	Acceptable
870.1300	Acute Inhalation Toxicity	49997801	IV	Acceptable
870.2400	Primary Eye Irritation	49997801	I	Acceptable
870.2500	Primary Dermal Irritation	49997801	IV	Acceptable
870.2600	Dermal Sensitization	49997801	Not a sensitizer	Acceptable

CONCLUSION:

The acute toxicity requirements have been satisfied for the subject product EPA Reg. No. 83019-4.

LABELING:

ID #: EPA Reg. No.: 083019-00004 / HM 4072 Antimicrobial

SIGNAL WORD: DANGER-POISON Skull & Crossbones required

RESTRICTED USE CLASSIFICATION TRIGGERED:

The criteria for Restricted Use Classification have been met due to Toxicity Category I for primary eye irritation.

HAZARDS TO HUMANS AND DOMESTIC ANIMALS:

Corrosive. Causes irreversible eye damage. Methanol may cause blindness. Do not get in eyes or on clothing. Wear protective eyewear such as goggles, face shield, or safety glasses. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet. Remove and wash contaminated clothing before reuse.

FIRST AID:

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice

IF SWALLOWED: Call poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact [insert phone number 1-800-xxx-xxxx] for emergency medical treatment information.

NOTE TO PHYSICIAN:

Probable mucosal damage may contraindicate the use of gastric lavage.

Note to PM/CRM/Registrant:

The proposed label should contain a Note to Physician which addresses the Toxicity Category I for primary eye irritation. The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (OPPTS 870.1100)

Product Manager: Eric Miederhoff / 31
MRID No.: 499978-01

Reviewer: B. Yurchak
Study Completion Date: 03/24/2016
Project No.: 19579-15

Testing Laboratory: Stillmeadow, Inc
Author: Theresa A. Hartwell, B.S.

Quality Assurance (40 CFR §160): Included

Test Material: *Ztrex 72 Antimicrobial Agent MUP*, clear liquid
Dosage: 5000 mg/kg

Species: Rat, Sprague-Dawley derived, albino strain
Sex: 3 Females
Age: 8-12 weeks
Weight: 173-191 grams
Source: Texas Animal Specialties; Humble, TX

Method: Up-and-Down Procedure

Summary:

1. **Estimated LD_{50}**: greater than 5000 mg/kg
2. **Toxicity Category**: IV
3. **Classification**: Acceptable

Deviations from Guideline 870.1100 and other comments: One animal weight was under protocol range; one animal was not observed within 30 minutes after dosing; relative humidity was at times outside protocol range. The deviations did not affect study outcome.

Procedure:

The test substance was administered by oral gavage to three healthy female rat using an initial limit dose of 5000 mg/kg. Due to no mortality in these animals, the study was terminated.

Observations:

There was no mortality during the study. Animals exhibited weekly weight gain during the study. All animals appeared normal for the duration of the study.

Reported Mortality – Limit Test

Dosing Sequence	Dose Level (mg/kg)	Short-Term Outcome	Long-Term Outcome
1	5000	O	O
2	5000	O	O
3	5000	O	O

O = Survival; X = Death

Gross Necropsy: Gross necropsy conducted at terminal sacrifice revealed no observable abnormalities.

Results: Under the conditions of this study, the acute oral LD_{50} of the test substance was determined to be greater than 5000 mg/kg.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (OPPTS 870.1200)

Product Manager: Eric Miederhoff / 31
MRID No.: 499978-01

Reviewer: B. Yurchak
Study Completion Date: 04/19/2016
Project No.: 19580-15

Testing Laboratory: Stillmeadow, Inc
Author: Theresa A. Hartwell, B.S.

Quality Assurance (40 CFR §160): Included

Test Material: *Ztrex 72 Antimicrobial Agent MUP*, clear liquid
Dosage: 5050 mg/kg

Species: Albino rat; Sprague-Dawley
Sex: 5 Males, 5 Females
Age: 12 weeks
Weight: Male: 249-289 g; Female: 170-193 g
Source: Texas Animal Specialties; Humble, TX

Summary:

1. **Estimated LD_{50}**: greater than 5050 mg/kg
2. **Toxicity Category**: IV
3. **Classification**: Acceptable

Deviations from Guideline 870.1200 and other comments: Relative humidity was at times outside protocol range; two female body weights were under protocol range. The deviations did not affect study outcome.

Preparation/Application:

5050 milligrams of the test substance per kilogram of body weight was applied evenly over a dose area of approximately 10% of the body surface and covered with a 2-inch x 4 inch, surgical gauze patch and secured with non-irritating adhesive tape. The gauze pad and entire trunk of each animal were the wrapped with a veterinary flexible cohesive bandage secured with non-irritating tape to avoid dislocation of the pad and to minimize loss of the test substance. After 24 hours of exposure to the test substance, the pads were removed and the test sites were gently cleansed to remove any residual test substance.

Observations:

Dermal application of the test substance at 5050 mg/kg to male and female rats produced no mortality during the 14-day observation period. All animals appeared normal for the duration of the study. Irritation included very slight to well-defined erythema, atonia and blanching through Day 11. All animals gained body weight over the 14-day observation period, except for one female that lost 2 g between Days 7 and 14.

Reported Mortality

Dose Level (mg/kg)	Number Dead / Number Tested		
	Males	Females	Combined
5050	0/5	0/5	0/10

Gross Necropsy Gross necropsy conducted at study termination revealed no observable abnormalities except for gas in intestines of one male.

Study Results:

The study results state that the dermal LD_{50} of the sample was > 5050 mg/kg in male and female rats.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3, 870.1300)

Product Manager: Eric Miederhoff / 31
MRID No.: 499978-01

Reviewer: B. Yurchak
Study Completion Date: 06/01/2016
Project No.: 19581-15

Testing Laboratory: Stillmeadow, Inc
Author: Andrew Doig, MS.

Quality Assurance (40 CFR §160.12): Included

Test Material: *Ztrex 72 Antimicrobial Agent MUP*, clear liquid
Species: Sprague-Dawley derived albino rats
Age: young adult, 8-12 weeks
Quantity & Sex: 5 males and 5 females
Weight: Male: 246-299 g; Female: 207-224 g
Source: Texas Animal Specialties; Humble, TX

Summary:

1. **LC_{50} (mg/L):** > 2.20 (male/female)

2. **MMAD (**µm**):** 3.0 **GSD (**µm**):** 2.0

3. **Tox. Category:** IV **Classification**: Acceptable

Procedure (Deviation From §81-3): Relative humidity was at times outside protocol range. The deviation did not affect study outcome.

Observations:

Five males and five females were exposed for 4 hours to an aerosol generated from undiluted liquid test substance at 2.20 mg/L. One animal died during the study. Clinical signs included activity decrease, fluid on muzzle, gasping, piloerection and sensitivity to sound, no longer evident by Day 6. In survivors, all except one male lost weight between Days 0 and 7. Gross necropsy revealed no observable abnormalities in terminated animals except for pale lungs in two; abnormalities in the animal that died during test pertained to lungs and content of intestines.

Results:

Reported Mortality

Exposure Concentration (mg/L)	(number deaths/number tested)		
	Males	Females	combined
2.20	1/5	0/5	1/10

Chamber Atmosphere		
Dose Level, mg/L	MMAD, µm	GSD, µm
2.20	2.8	3.5
2.20	3.3	2.4
mean	3.0	2.0

Chamber Environment	Dose Level, mg/L
	2.20
Chamber Volume, L	500
Gravimetric Concentration, mg/L	2.20
Nominal Chamber Concentration, mg/L	10.4
Airflow, Lpm	362
Temperature (˚C)	20-23
Relative Humidity %	41-83

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (OCSPP 870.2400)

Product Manager: Eric Miederhoff / 31
MRID No.: 499978-01

Reviewer: B. Yurchak
Study Completion Date: 4/19/2016
Project No.: 19582-15

Testing Laboratory: Stillmeadow, Inc
Author: Theresa A. Hartwell, B.S.

Quality Assurance (40 CFR §160): Included

Test Material: *Ztrex 72 Antimicrobial Agent MUP*, clear liquid

Dosage: 0.1 mL

Species: Rabbit, New Zealand albino strain
Sex: 2 males, 1 female
Age: 9-12 weeks
Weight: 2.2-2.2 kg / 2.9-3.2 kg
Source: Veterinary Clinical Resources; Hutto, TX

Method: OPP 81-4

Summary:

1. **Toxicity Category:** I
2. **Classification:** Acceptable

Deviations from Guideline 870.2400: Relative humidity was at times outside protocol range. The deviation did not affect study outcome.

Results:

The table below provides the results ("positive" irritation) following placing of 0.1 mL of the test material into the conjunctival sac of the right eye of each animal. There were no deaths or abnormal systemic clinical signs during the study.

	Time After Treatment									
	Hours					Day				
	1	24	48	72	4	7	10	14	17	21
Cornea										
Opacity	2/2*	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
Iritis	0/3	0/3	0/3	0/3	0/3	0/3	**	**	**	**
Conjunctivae										
Redness	0/3	3/3	2/3	3/3	3/3	2/3	2/3	0/3	0/3	0/3
Chemosis	3/3	3/3	3/3	3/3	3/3	2/3	2/3	1/3	1/3	1/3

* - Unable to score one animal due to severity of chemosis; ** - Unable to score due to severity of opacity

Positive effects persisted in all eyes through Day 21 after treatment. The test substance is rated extremely irritating and assigned Toxicity Category I.

DATA REVIEW FOR ACUTE DERMAL IRRITATION TESTING (OCSPP 870.2500)

Product Manager: Eric Miederhoff / 31
MRID No.: 499978-01

Reviewer: B. Yurchak
Study Completion Date: 3/24/2016
Project No.: 19583-15

Testing Laboratory: Stillmeadow, Inc
Author: Theresa A. Hartwell, B.S.

Quality Assurance (40 CFR §160): Included

Test Material: *Ztrex 72 Antimicrobial Agent MUP*, clear liquid
Dosage: 0.5 mL

Animals: Rabbit, New Zealand albino strain
Sex: 3 Females
Age: 9-11 weeks
Weight: 2.3-2.8 kg
Source: Veterinary Clinical Resources; Hutto, TX

Method: OPP 81-5

Summary:

1. **Toxicity Category:** IV PII = 1.6
2. **Classification:** Acceptable

Deviations from Guideline 870.2500: Relative humidity was at times outside protocol range. The deviation did not affect study outcome.

Results:

The table below provides the results (individual Draize scores) from four-hour dermal exposures of three rabbits to 0.5 mL of the undiluted test material under a 2.5 x 2.5 cm gauze parch that was placed over to intact clipped dorsal trunk. Very slight to well-defined erythema was present at each observation through Day 10. Very slight edema was present at 48 hours through Day 10. Other dermal effects included atonia and desquamation; staining of the site was also noted. The Primary Irritation Index was 1.6, making the test material slightly irritating (U.S. EPA, 1988). There were no deaths or abnormal systemic clinical signs during the study.

Individual Dermal Irritation Scores following the four-hour exposure

Animal No.	Sex	Erythema / Edema			
		Time After Patch Removal			
		30-60 minutes	24 hours	48 hours	72 hours
0031	F	1 / 0	1 / 0	1 / 1	1 / 1
0029	F	1 / 0	1 / 0	1 / 1	1 / 1
0021	F	1 / 0	1 / 0	1 / 1	2 / 1

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (OPPTS 870.2600)

Product Manager: Eric Miederhoff / 31
MRID No.: 499978-01

Reviewer: B. Yurchak
Study Completion Date: 04/19/2016
Project No.: 19584-15

Testing Laboratory: Stillmeadow, Inc
Author: Theresa A. Hartwell, B.S.

Quality Assurance (40 CFR §160): Included

Test Material: *Ztrex 72 Antimicrobial Agent MUP*, clear liquid

Animals: Guinea pig, Hartley albino
Test group: 10 males and 10 females
Naïve control: 5 males and 5 females
Preliminary irritation testing: 2 males and 2 females
Weight: 365-554 grams
Source: Charles River, Hdq; Wilmington, MA

Historical Positive Control:
Substance: Alpha-Hexylcinnamaldehyde, 85%: 0.4 mL
Animals: Guinea pig, Hartley albino
Test group: 5 males and 5 females

Method: Buehler

Summary:

1. *Ztrex 72 Antimicrobial Agent MUP* was a Non-sensitizer.
2. **Classification**: Acceptable

Deviations from Guideline 870.2600 and other comments: Relative humidity and temperature were at times outside protocol range; nine animal weights were over protocol range. The deviations did not affect study outcome.

Procedure:

The test substance was administrated by application of 0.4 mL of the undiluted test substance to 20 healthy test guinea pigs, once each week for 3-week induction period. Twenty-seven (27) days after the first induction dose, a challenge dose of the test substance at its determination of highest non-irritating concentration was applied to a naive site on each guinea pig. A naive control group (10 animals) was maintained under the same environmental conditions and treated with the test substance at challenge only. Approximately 24 and 48 hours after each induction and challenge dose, the animals were scored for Erythema and Edema.

Results:

The test substance produced no reactions in either Test animals or Naïve control animals after the challenge treatment. No reactions were noted also after the induction treatments. Based on the study findings, Ztrex 72 Antimicrobial Agent MUP was not considered to be a contact sensitizer. Positive Control study results were appropriate.

Response Indices – Erythema at Challenge – Sterilex Ultra Powder

	Incidence of Positive Response[1]		Severity[2]	
	24 Hrs	**48 Hrs**	**24 Hrs**	**48 Hrs**
Test Group	0 / 20	0 / 20	0.0	0.0
Naïve Control Group	0 / 10	0 / 10	0.0	0.0

[1] Number of erythema scores greater than 0.5 per number of animals evaluated.
[2] Sum of the erythema scores divided by the number of animals evaluated.